8. Two cases of the development of penicillin resistance in *Staph. pyogenes* following a break in treatment are reported.

9. The frequency of application, strength of the emulsion, suitable base and type of cases treated are discussed.

CONCLUSION

Penicillin used in an emulsion base offers a real advance in treatment of superficial skin infections. However, bacteriological investigation must be done in every case to determine the organism and its penicillin sensitivity, otherwise a valuable remedy is wasted. Nothing will discredit penicillin more than its indiscriminate use by over-enthusiastic investigators.

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ACUTE FLUORIDE POISONING*

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RECENTLY, the writer was consulted about treatment of acute fluoride poisoning, in view of the increasing use of fluorine and fluorine-containing compounds in industries. In outlining the treatment recommended, a point which was stressed was that, aside from death due to the corrosive action of the poison, death may result very rapidly from reduction of the calcium content of the blood.

A number of textbooks on toxicology in the English language do not mention fluoride poisoning.[1, 2, 3, 4] A recent and widely-used textbook on therapeutics does not mention it,[5] and, though all of the textbooks which were investigated and in which fluoride poisoning is described mention signs and symptoms which may be caused by reduction of the calcium content of the blood, five only[6 to 10] associate them with a disturbance of calcium, though textbooks on pharmacology have done so for some time. In the 4th edition of Sollmann's Pharmacology[11] it is stated that "the acute effects may be due partly to disionization of calcium, similar to oxalates" and it is suggested that "intravenous injection of calcium chloride might be useful". In Webster's Legal Medicine and Toxicology[6] there is the statement that fluorine "combines with the calcium of the tissues and becomes, therefore, a protoplasmic poison". In Leschke's Clinical Toxicology[7] it is stated that "sodium-fluoride produces disorders of the calcium metabolism similar to those which occur after removal of the para-thyroid glands". In the recent (8th) edition of Sydney Smith's Forensic Medicine[8] it is pointed out that, in addition to their corrosive action, fluorides are "generally protoplasmic poisons closely allied to the oxalates" and, under "oxalates" (p. 448) it is stated that there is every reason to believe that the action of oxalic acid is "partially or wholly due to the combination of the acid with the calcium salts of the blood and tissues, thus rendering the essential calcium ions inoperative". The resemblance to oxalates is also mentioned by Underhill and Koppanyi.[9] The fact that acute fluoride poisoning may have a serious effect upon the calcium content of the blood is dealt with at some length in McNally's Toxicology.[10]

Of the above-mentioned five books in which there is reference to possible disturbances of calcium metabolism, two only[8, 10] deal with the necessary treatment. The others, in common with all books in which acute fluoride poisoning is mentioned, recommend use of calcium-containing compounds by mouth before and during gastric lavage; but this, as is either specifically stated[6, 9, 12] or is obvious otherwise,[13, 14, 15] is merely for the purpose of converting the ingested fluoride into insoluble calcium fluoride and thus preventing further absorption of the poison and corrosive action locally. In their Pharmacological Basis of Therapeutics[16] Goodman and Gilman also mention use of calcium salts only for the purpose of precipitating the unabsorbed fluoride. In Sydney Smith's Forensic Medicine[8] the author recommends transfusion of a neutral calcium salt, such as calcium gluconate when "the general effects appear to be due to the withdrawal of calcium from the fluids and tissues of the body".

McNally[10] recommends calcium gluconate "intravenously immediately after washing out the stomach". The extremely urgent need of such treatment, at times, may be seen in the experiences with a fatal case in the Montreal General Hospital. The patient was moribund and died before calcium gluconate could be administered. The case is, however, instructive because of (*a*) the extremely low blood calcium and (*b*) the slight degree of corrosion of the stomach, which clearly indicated that death was not due to the corrosive action of the poison but largely to the reduction of the calcium content of the blood. The following are, briefly, the facts of the case.

A man, aged 39, was admitted to the out-door department of the Montreal General Hospital with a history of having attempted suicide by ingestion of sodium fluoride. Though, in "shock", he was able to tell the intern on duty what he had taken and when he had taken it. He also stated that, soon after he had taken the poison, he began to have "muscle spasms" in the feet and hands. *He did not vomit.* When the intern saw him, the striking features were salivation, low blood pressure and "spasm of the hands resembling the carpal spasm of tetany". The stomach was washed thoroughly and about 15 gm. of calcium lactate were left in the stomach. He lost consciousness

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rapidly and died from respiratory failure three hours and five minutes after ingestion of the poison. A sample of blood, taken a few minutes before he died, showed 2.6 mgm. only of calcium per 100 c.c. of serum, which, as far as I have been able to ascertain, is the lowest value ever found in a human being. (Normal = 9 to 11.5 mgm. per 100 c.c.)

At the autopsy (by the coroner) the only evidence that a corrosive poison had been taken was a small area of swelling of the mucosa of the stomach near the duodenum, which fitted in with the complete absence of vomiting both before and after his admission to the hospital. A case with no gastro-intestinal symptoms has been reported by McNally.[10]

Before describing treatment recommended in such cases, an attempt will be made to summarize briefly the essential facts about fluorine and fluorine-containing compounds and their toxicology, in view of the increasing use of these compounds in industries.

OCCURRENCE

Fluorspar (CaF_2), a naturally occurring fluorine compound, has been known since 1529. It was first used for etching of glass in 1670[17] and has been used extensively for this purpose since then. Clouding of electrical bulbs is an example. It is used extensively as a flux in smelting metals, during which volatile silicon tetrafluoride (SiF_4) is a by-product. Enormous quantities of cryolite (Na_3AlF_6) are used for production of aluminium, and, during this process, highly volatile hydrofluoric acid (HF) is an unavoidable by-product. Phosphate rock, which contains about 3.5% fluorine, is used for manufacture of superphosphate used in animal and plant nutrition. Fluorides are required for manufacture of organic fluorides, and they are constituents of insecticide sprays and powders and of rat poison. Rubber, textile, ceramic, hide and skin, enamel, cement, glue, brick, wood, refrigeration and magnesium casting are examples of other industries in which fluorides are used.

TOXICOLOGY

Types of poisoning.—These may be considered under three headings, namely, (*a*) fluorine gas; (*b*) hydrofluoric acid, and (*c*) soluble salts of fluorine. Their importance as poisons is in the reverse order. Acute fluorine gas poisoning is so rare that it needs only mere mention; whereas, most of the deaths, accidental and suicidal, have been due to sodium fluoride and other soluble fluoride salts.

Fluorine. — This is one of the most active elements, combining very readily with metals and, therefore, does not occur in a free state in nature. It reacts very readily with the moisture in the air to form hydrofluoric acid. Industrially, therefore, the hazard, as in production of aluminium from cryolite, is not from the element but from the acid.

Fluorine is a light, greenish-yellow gas and produces intense irritation of the conjunctivæ and mucous membranes of the air passages, causing violent spasms of coughing, with pain in the chest, which may persist for some time after the victim has been removed to fresh air. The most serious effects are upon the lungs. The exact mechanism is not clear. Experiences with chlorine gas in the Great War and since then have shown that the most serious results, such as pulmonary œdema, are not explained entirely by production of a corrosive acid, and there is reason to believe that this also applies to fluorine.

Treatment. — Fresh air, warmth, rest, hot sweet drinks and oxygen immediately for any degree of cyanosis. Experiences with lung irritant gases in the last war showed that no person in whom it was possible to restore a pink colour by proper use of oxygen died from simple pulmonary œdema.[18] Even mild cases should be kept under observation for the first 24 hours for the possibility of delayed onset of pulmonary œdema.[19]

Hydrofluoric acid.—This is a colourless liquid which fumes in air. It is a violent poison, both in itself and also because the commercial product may contain sulphuric acid. It irritates all tissues with which it comes into contact. The solutions used for etching of glass contain anywhere from 15 to 40% of hydrofluoric acid.

(*a*) *Inhalation.* — Inhalation of hydrofluoric acid fumes in very high concentrations may produce vomiting and rapid collapse. In lesser concentrations, they produce inflammation and ulceration of the conjunctivæ and of the mucous membranes of the nose, mouth, larynx and bronchi. As little as 10 parts of the acid per 1 000,000 parts of air has produced such ulcerative lesions and broncho-pneumonia.[20] For treatment, see fluorine.

In lower concentrations for short periods, except for temporary cough and lachrymation, which soon passes off in fresh air, the fumes are apparently harmless. The maximum allowable concentration for prolonged exposure is about 2.5 mgm. per cubic metre or, approximately, three parts of the gas per 1,000,000 parts of air.[21, 22] Prolonged and repeated exposure to

mildly irritant concentrations seems to decrease the sensitivity to the fumes. A personal experience may be cited here as an example. While visiting an aluminium production plant, the writer found the fumes very uncomfortable; they produced marked lachrymation, a sensation of suffocation and cough which continued for about one-half hour after having left the contaminated atmosphere; whereas, no discomfort was noticed amongst the many workers, none coughed, and none showed any lachrymation.

(*b*) *Ingestion.*—Hydrofluoric acid, when taken by mouth, is a violent corrosive poison. The chief features are marked dysphagia, vomiting and collapse, and death may occur within a few minutes. The buccal mucosa may be bleached and there may be denudation of the epithelium of the tongue, pharynx and œsophagus. Even in contact with skin such solutions produce blisters and gangrene. The burns are painful and heal slowly.

The minimum lethal dose by mouth is not known. One tablespoonful of a 9% solution has caused death.[6] When death does not occur within an hour, in addition to the signs and symptoms due to the corrosive action locally, there may be also those produced by reduction of the calcium content of the blood and by direct action of the poison on the heart muscle. For signs of the latter and treatment, see below.

FLUORIDE SALTS

Most deaths, accidental and suicidal, have been due to these compounds. Sodium fluoride heads the list, and the description of it here applies, in general, to the other soluble salts.

Fluorine is widely distributed in nature. It is, therefore, a constituent of normal body tissues, particularly teeth and bone; but, like lead, it is present in minute traces and probably as a contamination rather than for physiological needs. Sodium fluoride is a corrosive and a general protoplasmic poison. It is poisonous to plants and bacteria and inhibits enzyme action (urease, lipase, etc.). It combines with calcium in an ionic state to form insoluble calcium fluoride. Calcium, as is well known, is indispensable for the functional integrity of the voluntary and autonomic nervous systems; but only calcium in ionic form is physiologically active, and it is precisely such calcium which is attacked by fluorides. Sodium fluoride thus lowers the available calcium of the blood and thus produces low-calcium tetany. For the same reason, sodium fluoride is an anticoagulant, but also probably by an effect upon thrombin formation and also injury to the liver. Normal coagulation, for example, is not restored by replacing the calcium lost by precipitation but only if thrombin is also added.[11]

Sodium fluoride is not very soluble (a saturated solution contains, approximately, 4 grams per 100 c.c.) but, when in solution, it is rapidly absorbed from the stomach. Destruction of the mucous membrane lining of the stomach increases the absorption. Unlike the other halogens (chlorine, bromine and iodine), however, it is slowly excreted and thus tends to accumulate in the body tissues as insoluble calcium fluoride, which tends to deposit in the liver, kidneys and other tissues, as readily recognizable crystals. When deposited in bone, the calcium fluoride makes the latter white, harder and more brittle. Unlike oxalic acid, which also combines with, and thus lowers, the available calcium in the blood, sodium fluoride also exerts an alkaloid-like reaction. In lower organisms, for example, which do not require calcium, the fluorides still exert this action; whereas, oxalic acid does not.

Fatal dose.—The minimum lethal dose is not known. About 4 gm. have caused death in an adult. In general, the more soluble the fluoride the greater is its toxicity; but fluorine content is an equally important factor. Sodium fluosilicate (Na_2SiF_6) for example, used widely as a rat poison, is much less soluble than sodium fluoride, but, when adjusted to fluorine content, the toxicity is approximately the same. As little as 0.2 to 0.7 gm. of sodium fluosilicate have caused death in adults.[23]

Fatal period.—Though the salts tend to act more slowly than hydrofluoric acid, death has resulted within 5, 10 and 15 minutes,[6, 24, 25] but periods of 10 to 12 hours have been noted. In the case cited above, death occurred in three hours. The average is about eight hours.

Post-mortem appearances. — Depending upon the degree of irritation and corrosion, the appearance of the mucosa of the stomach may vary from that of slight inflammation only to dark crimson discoloration of the rugæ, marked œdema, hæmorrhage and necrosis with marked blackening. Changes in the muscularis are, however, rare. If death has not occurred for some time, similar changes may be noted in the duodenum and jejunum. The liver and kidneys may show extensive and severe parenchymatous changes and, as stated, may contain crystalline

deposits of calcium fluoride. As much as 1.6 mgm. of CaF_2 per 100 gm. of soft tissue has been found in a fatal case, compared with the "normal" 20 to 80 micrograms.[26]

Signs and symptoms.—As a rule, the initial signs and symptoms are produced by the corrosive action of the poison—burning sensation in the mouth, dysphagia, great thirst, salivation, abdominal pain, nausea, and vomiting. As the corrosive effects become more marked, there is diarrhœa; the vomitus and fæces may contain blood, and death may result from shock; but, as in the case cited above, the dominant signs and symptoms may be those of a lowered blood calcium—stiffness of muscles, paralysis of the facial muscles, inability to talk, inability to walk, classical low-calcium tetany of the hands and feet, epileptiform convulsions, etc. Death may then occur from asphyxia due to fixation of the respiratory muscles. In a series of 34 cases, convulsions occurred in 11, approximately 33%.[24] Fluorides also have a direct toxic action on heart muscle and thus may reduce the blood pressure, independent of shock, and cause death from heart failure.

Treatment.—Administer lime water immediately. Then wash the stomach thoroughly with lime water. If lime water is not available, a weak solution of calcium chloride (one teaspoonful to a quart of water) is equally effective, but is an irritant. If neither lime water nor calcium chloride is available, use milk. If water only must be used, the stomach should be washed *repeatedly* with *small* amounts. (The more dilute the poison—the lower the osmotic pressure—the more rapidly does the poison leave the stomach and, therefore, the greater is the danger of its being absorbed into the system).

Inject slowly 10 c.c. of a 10% solution of calcium gluconate intravenously and repeat the injection without delay on appearance of any signs suggestive of tetany (see above). If calcium gluconate is not available, a 10% solution of calcium chloride may be used, but the latter must be injected *very slowly*. Calcium gluconate contains about 9% only of calcium; whereas, calcium chloride contains about three times as much. With the latter, therefore, there is a greater danger of a high concentration of calcium reaching the heart and thus producing cardiac syncope. Calcium chloride also irritates the veins more than the gluconate. *Never inject calcium chloride into the subcutaneous tissues.* It should be noted here also that the injection of calcium tends to cause vasodilatation. It, thus, also tends to lower blood pressure and precipitate shock or aggravate it; but the danger is much less than the danger from the effects of the poison.

To prevent shock from severe pain, administer at once 1/6 grain morphine intravenously. Treat any shock present very energetically. Place the patient in a head-low posture and administer oxygen for *any* degree of cyanosis. Inject intravenously 50 c.c. of a 50% solution of glucose; then, by a continuous drip, inject one to two litres of a 10% glucose solution at a rate of 2 to 10 c.c. per minute; depending upon the degree of shock. Unlike "traumatic" shock, direct cardiac stimulants may be useful, because of effects of the poison on heart muscle. Do not use adrenalin, which tends to aggravate shock by causing further capillary dilatation. Caffeine-sodium-benzoate (7½ gr.) intravenously is useful.

After the stomach has been washed thoroughly and the necessary measures have been taken against tetany and shock, milk and egg white should be administered and continued at frequent intervals during the first 48 hours; also, calcium lactate (about 5 gm.) every four hours combined with twice the quantity of lactose, which it appears enhances the antispasmodic action of calcium.

Detection of poison.—Though it is not the purpose here to deal with this aspect of fluoride poisoning, an experience some time ago is of interest. During the preliminary distillation of the suspected material, after acidification, the entire distilling apparatus, flask and condenser, suddenly became opaque with a frost-like coating. What had happened was that the acid used to acidify the mixture combined with the fluoride and thus produced hydrofluoric acid which etched the glass. The fact, therefore, that the suspected material contained a fluoride became obvious immediately.

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Medical Arts Bldg.

MENTAL ILLNESS AND THE PRINCIPLES OF MEDICINE

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THE human being in action is conditioned by physical, psychological and constitutional factors. Each individual inherits certain psychophysical tendencies or trends on which mental and physical stresses are continually acting. The health of the individual depends both on the relative strength of these constitutional factors and the environmental factors acting upon them. In the realm of mental disorder two individuals may be faced with apparently the same series of psychological and physical challenges, yet one may break down while the other may adjust satisfactorily. This would indicate that the constitutional factors were the determining ones. Again, if two individuals of equal constitutional robustness are confronted by physical or psychological strain, ill health will be determined by the strength of the environmental stress. Therefore in every case these three aspects must always be assessed. The omission of any one in the investigation of a case may lead to a wrong diagnosis and management.

It is necessary to guard against an initial prejudice in favour of any one of these factors. Mental symptoms may so dominate the clinical picture that they tend to mask a possible underlying physical disturbance with the result that the physical aspect not infrequently is the one to be omitted in the assessment of a mental illness. To illustrate this point, to emphasize the interaction and importance of all three determinants, and to show that mental illness and its investigation complies with the general principles of medicine, the following cases are presented:

CASE 1

This man, aged 41, was admitted to the Toronto Psychiatric Hospital on a magistrate's warrant. His manner had been peculiar for some time. He had finally struck his wife. On the advice of the physician she laid a charge of assault. On admission he appeared confused, unsteady and acted as if intoxicated. Memory for recent events was poor. He was untidy and would get out of bed and urinate on the floor. At times he would complain of severe headaches, sudden in onset and offset.

Investigation of this man's past history indicated he had been well adjusted, jolly, happy-go-lucky and had had many friends. He was working as a florist's assistant until December, 1935 (14 months previously) when he had a difference of opinion with his employer regarding overtime and was given a week's pay and discharged. He could not find work and developed moody spells and would sit by himself for long periods. His behaviour would frequently be silly; he would laugh for no apparent reason and when questioned would make irrelevant remarks. In August, 1936 (*i.e.*, 6 months previous to admission) it was noticed by the patient's family that his "eyes turned in" and the patient complained of seeing double. His mental symptoms became more pronounced, he brooded, and would sit staring into space. Since October, 1936, he often cried out, "My head, my head", and then would laugh. The last few weeks previous to admission, patient stated that he expected the devil daily at 3.00 p.m. He thought people were outside the window. He complained of crawling feelings up the back of his head. He misidentified relatives and his wife became afraid of him and finally laid a charge of assault when he slapped her.

Examination.—Internal strabismus of the right eye. Pupils reacted, but right sluggishly. Question of slight weakness of right grip. Inclined to fall to right. Badly choked optic discs. No other neurological signs. Urine showed one plus sugar. Hæmoglobin 98%; temperature 97 to 98°; pulse 80 to 84; blood pressure 100/70; Wassermann and Kahn test negative.

A frontal lobe tumour was suspected and patient was transferred to the Toronto General Hospital on February 18, for operation. The surgeon found a large meningioma (the size of an orange and weighing 105 grams) in the midline about the frontal region and growing from longitudinal sinus and falx and impinging on both frontal lobes. Patient did not survive the operation.